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Thanatophoric Dysplasia

Tegan French, BMBS[1] and Ravi Savarirayan, MBBS, MD, FRACP, ARCPA (Hon)[2]

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Summary

Clinical characteristics

Thanatophoric dysplasia (TD) is a short-limb skeletal dysplasia that is usually lethal in the perinatal period. TD is divided into subtypes:

- TD type 1 is characterized by micromelia with bowed femurs and, uncommonly, the presence of craniosynostosis of varying severity.
- TD type 2 is characterized by micromelia with straight femurs and uniform presence of moderate-to-severe craniosynostosis with cloverleaf skull deformity.

Other features common to type 1 and type 2 include: short ribs, narrow thorax, relative macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die of respiratory insufficiency shortly after birth. Rare long-term survivors have been reported.

Diagnosis/testing

The diagnosis of TD is established in a proband with characteristic clinical and/or radiologic features and/or a heterozygous pathogenic variant in *FGFR3* identified on molecular genetic testing.

Management

Treatment of manifestations: Most individuals with TD die in the perinatal period because of the multisystem complications of the disorder. Management goals should be established with the family and may focus on provision of comfort care. Newborns require long-term respiratory support (typically with tracheostomy and ventilation) to survive. Anesthetic management guidelines for skeletal dysplasias are applicable to individuals with TD. Other treatment measures may include shunt placement for hydrocephalus, suboccipital decompression for relief of craniocervical junction constriction, anti-seizure medication to control seizures, and hearing aids.

Author Affiliations: 1 Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia; Email: tegan.french@vcgs.org.au. 2 Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Royal Children's Hospital; University of Melbourne, Melbourne, Australia; Email: ravi.savarirayan@vcgs.org.au.

Surveillance: Long-term survivors need neuroimaging to monitor for craniocervical constriction, assessment of neurologic status, and EEG to monitor for seizure activity, as well as developmental, orthopedic, and audiology evaluations.

Pregnancy management: When TD is diagnosed prenatally, treatment goals are to avoid potential pregnancy complications including prematurity, polyhydramnios, malpresentation, and delivery complications from macrocephaly and/or a flexed and rigid neck; cephalocentesis and cesarean section may be considered to avoid maternal complications.

Genetic counseling

TD is inherited in an autosomal dominant manner; the majority of probands have a *de novo FGFR3* pathogenic variant. Risk of sib recurrence for parents who have had one affected child is not significantly increased over that of the general population. Germline mosaicism in healthy parents, although not reported to date, remains a theoretic possibility. Prenatal diagnosis is possible by ultrasound examination and molecular genetic testing.

GeneReview Scope

Thanatophoric Dysplasia: Included Phenotypes
• Thanatophoric dysplasia type 1 (*FGFR3*-related thanatophoric dysplasia type 1) • Thanatophoric dysplasia type 2 (*FGFR3*-related thanatophoric dysplasia type 2)

For synonyms and outdated names, see Nomenclature.

Diagnosis

Formal diagnostic criteria for thanatophoric dysplasia (TD) have not been established.

Suggestive Findings

TD **should be suspected** in a fetus with the following prenatal imaging findings, or a neonate with the following clinical and radiographic features.

Prenatal ultrasound examination [Tonni et al 2010, Khalil et al 2011, Martínez-Frías et al 2011, Bondioni et al 2017] findings by trimester:

- First trimester
  - Shortening of the long bones, possibly visible as early as 12 to 14 weeks' gestation
  - Increased nuchal translucency
- Second/third trimester
  - Growth deficiency with limb length below fifth centile recognizable by 20 weeks' gestation
  - Well-ossified spine and skull
  - Platyspondyly
  - Ventriculomegaly
  - Narrow chest cavity with short ribs
  - Polyhydramnios
  - Bowed femurs (TD type 1)
  - Brain anomalies
  - Cloverleaf skull. Craniosynostosis involving coronal, lambdoid, and sagittal sutures, resulting in a trilobed skull shape (previously referred to as *Kleeblattschädel* (often in TD type 2; occasionally in TD type 1)
  - Relative macrocephaly

Postnatal physical examination

- Relative macrocephaly
- Cloverleaf skull (always in TD type 2; sometimes in TD type 1)
- Large anterior fontanelle
- Frontal bossing, flat facies with a depressed nasal bridge, ocular proptosis
- Marked shortening of the limbs (micromelia)
- Redundant skin folds
- Narrow bell-shaped thorax with short ribs and protuberant abdomen
- Relatively normal trunk length
- Brachydactyly with trident hand
- Bowed femurs (TD type 1)
- Generalized hypotonia

Radiographs / other imaging studies [Wilcox et al 1998, Lemyre et al 1999, Bondioni et al 2017]

- Rhizomelic shortening of the long bones
- Irregular metaphyses of the long bones
- Platyspondyly
- Small foramen magnum with brain stem compression
- Bowed femurs (TD type 1)
- Cloverleaf skull (always in TD type 2; sometimes in TD type 1)
- CNS abnormalities including temporal lobe malformations, hydrocephalus, brain stem hypoplasia, neuronal migration abnormalities [Wang et al 2014]

Other rarely reported findings that are not part of the core phenotype include cardiac defects, renal abnormalities, and abnormalities of lymphatic development (see Clinical Characteristics).

Establishing the Diagnosis

The diagnosis of thanatophoric dysplasia **is established** in a proband with the above clinical and radiographic features and/or a heterozygous pathogenic (or likely pathogenic) variant in *FGFR3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *FGFR3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (targeted analysis, single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of thanatophoric dysplasia is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other lethal skeletal dysplasias are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of thanatophoric dysplasia, molecular genetic testing approaches can include **targeted analysis**, **single-gene testing**, or use of a **multigene panel**.

Targeted analysis

- If TD type 2 is suspected on the basis of straight femurs and cloverleaf skull, targeted testing for the p.Lys650Glu pathogenic variant identified in >99% of individuals with TD type 2 may be an appropriate first step. Sequence analysis of *FGFR3* exon 15 can be considered next if no pathogenic variant is identified.
- If TD type 1 is suspected, sequence analysis of *FGFR3* can be considered.

Single-gene testing. Sequence analysis of *FGFR3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: (1) Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. (2) Since TD occurs through a gain-of-function mechanism and large intragenic *FGFR* deletion or duplication has not been reported, testing for intragenic deletions or duplication is unlikely to identify a disease-causing variant.

A skeletal dysplasia multigene panel that includes *FGFR3* and other genes of interest (see Differential Diagnosis) can be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other lethal skeletal dysplasias, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of TD.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Thanatophoric Dysplasia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FGFR3	Targeted analysis for p.Lys650Glu	>99% of probands w/TD type 2 [3, 4]
	Targeted analysis for p.Arg248Cys & p.Tyr373Cys	~90% of probands w/TD type 1 [4]
	Sequence analysis [5]	>99% [4, 6]
	Gene-targeted deletion/duplication analysis [7]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Xue et al [2014]
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and Xue et al [2014] (See Genotype-Phenotype Correlations.)
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. TD due to two *FGFR3* pathogenic variants *in cis* has been reported [Pannier et al 2009, Marquis-Nicholson et al 2013]. In both instances one pathogenic variant was previously reported to be associated with hypochondroplasia and one was a novel pathogenic missense variant.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

The clinical and radiographic features of thanatophoric dysplasia (TD) types 1 and 2 are evident prenatally or in the immediate newborn period. Respiratory insufficiency typically results in early neonatal death, and is due to a small chest cavity and/or foramen magnum narrowing with brain stem compression. However, long-term survivors have been reported, including rare reports of survival to adulthood with aggressive ventilatory support and surgical management of neurologic complications.

To date, more than 200 individuals with TD have been identified with a pathogenic variant in *FGFR3* [Xue et al 2014]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Thanatophoric Dysplasia

Feature	% of Persons w/Feature	Comment
Respiratory insufficiency	100%	Long-term survivors have all required mechanical ventilation.
Foramen magnum narrowing	~100% [1]	
Temporal lobe dysplasia	~100% [1, 2]	
Hydrocephalus	56% [2]	
Cloverleaf skull (multiple craniosynostosis)	100% in persons w/TD type 2; rarely in persons w/TD type 1	
Dysmorphic facial features	100%	Frontal bossing, flat facies, depressed nasal bridge, ocular proptosis
Relative macrocephaly	100%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Growth deficiency	100%	• Birth length well < 3rd centile • Birth weight & head circumference may be normal, but growth restriction of these parameters occurs in infancy & childhood.
Bowed femurs	100% in persons w/TD type 1; absent in persons w/TD type 2	
Survival past age 1 yr	5 persons [3]	Reports exist of long-term survivors into adulthood, all of whom have required long-term mechanical ventilation.

1. Hevner [2005]
2. Wang et al [2014]
3. Five long-term survivors reported [MacDonald et al 1989, Baker et al 1997, Katsumata et al 1998, Kuno et al 2000, Nikkel et al 2013]

Respiratory insufficiency. Most affected infants die of respiratory insufficiency in the first hours or days of life. Respiratory insufficiency may be secondary to a small chest with lung hypoplasia and/or compression of the brain stem due to a small foramen magnum. Some affected children have survived into childhood, universally requiring tracheostomy and aggressive ventilatory support. Nikkel et al [2013] described a long-term survivor with TD at age 28 years. Her course was exceptional, as she did not require invasive ventilatory support until age four months and required full-time ventilatory support from age 15 years.

Neurologic complications include small foramen magnum with brain stem compression, brain malformations (predominantly involving the temporal lobe), hydrocephalus, seizures, and profound developmental impairment in rare long-term survivors.

One infant reported at age 11 months required suboccipital decompression due to clonus and decreased limb movements secondary to a narrow foramen magnum [Thompson et al 2011]. One individual reported at age 28 years underwent surgical decompression of a small foramen magnum and insertion of a ventriculoperitoneal shunt [Nikkel et al 2013]. Despite this intervention, the individual developed cervical spinal cord compression and quadriplegia.

Temporal lobe malformations and megalencephaly are likely universal [Hevner 2005, Itoh et al 2013]. Temporal lobe abnormalities include enlargement, abnormal gyration and sulcation, polymicrogyria, and hippocampal abnormalities. Hydrocephalus is also common [Hevner 2005].

Brain malformations are the most likely etiology of seizures in individuals with TD; however, additional complications such as hypoxia related to respiratory insufficiency may also play a role.

Severe developmental delay is reported, with a stall in developmental progress at a developmental age of 12-20 months (see Table 3). Motor skills may be more significantly impaired due to the skeletal features and micromelia. Later deterioration in abilities following complications such as cord compression is described [Nikkel et al 2013].

Less common neurologic findings include hypoplasia or agenesis of the corpus callosum. Encephalocele has been reported, likely as a secondary consequence of raised intracranial pressure and abnormal skull formation [Martínez-Frías et al 2011].

Craniofacial. Relative macrocephaly is present at birth. Craniosynostosis with cloverleaf skull in individuals with TD type 2 contributes to hydrocephalus and neurologic complications. Dysmorphic facial features including frontal bossing, flat facies, depressed nasal bridge, and ocular proptosis are present.

Musculoskeletal complications in long-term survivors include kyphosis, osteopenia, and both joint hypermobility and joint contractures.

Growth deficiency. Prenatal short-limb short stature is present in all individuals. Growth deficiency persists with micromelia and redundant skin folds. Global growth deficiency is present in long-term survivors (see Table 3).

Integument. Extensive acanthosis nigricans has been reported with development of seborrheic keratoses in adult survivors [Nakai et al 2010, Nikkel et al 2013].

Hearing impairment is reported in several long-term survivors (see Table 3), but the etiology is not clear. The presence of midface hypoplasia in individuals with TD type 1, and recognition that *FGFR3* may be implicated in inner ear development [Colvin et al 1996], suggest that hearing loss in individuals with TD type 1 may be multifactorial.

Vision. Intermittent exotropia has been reported in a long-term survivor [Nikkel et al 2013].

Other rarely reported findings that do not have a proven association with TD include:

- Cardiac defects. Truncus arteriosus, ventricular septal defect, and patent foramen ovale have been reported [McBrien et al 2008]. Bradycardia has been reported in two individuals [Baker et al 1997, Nikkel et al 2013].
- Renal abnormalities [Prontera et al 2006]. In two long-term survivors, renal calculi were reported [Baker et al 1997, Kuno et al 2000].
- Protein losing enteropathy with intestinal lymphangestasia, reported in one individual [Yang & Dehner 2016]. An infant with TD was reported to have chylous ascites [Soo-Kyeong et al 2018].

Table 3. Thanatophoric Dysplasia: Clinical Features of Long-Term Survivors

	Long-Term Survivor: Sex, Age at Report				
	Male, age 4.75 yrs [1]	Female, age 28 yrs [2]	Male, age 9 yrs [3]	Female, age 23 yrs [4]	Male, age 8 yrs [5]
Method of diagnosis	Clinical / radiographic	Molecular (p.Arg248Cys)	Molecular (p.Arg248Cys)	Molecular (p.Arg248Cys)	Molecular (p.Gly370Cys)
Ventilated from age	Neonate	2 mos	9 yrs	ND	2 days
Estimated developmental age	2 mos	8-18 mos as a teenager [6]	18 mos	ND	10-12 mos
Neurologic	• Hydrocephalus requiring shunt • Suboccipital decompression • Seizures	• Hydrocephalus requiring shunt • Suboccipital decompression • Seizures	• Mild ventriculomegaly • Marked stenosis of skull base & upper cervical spine • Clinically suspected high cervical myelopathy but no surgery • Seizures	ND	ND
Skin	ND	Acanthosis nigricans & seborrheic keratoses	Acanthosis nigricans	Acanthosis nigricans & seborrheic keratoses	Acanthosis nigricans

Table 3. continued from previous page.

	Long-Term Survivor: Sex, Age at Report				
	Male, age 4.75 yrs [1]	Female, age 28 yrs [2]	Male, age 9 yrs [3]	Female, age 23 yrs [4]	Male, age 8 yrs [5]
Hearing	Hearing impairment	• Significant hearing impairment • Cholesteatoma	• Mixed hearing impairment • Bilateral hearing aids	ND	ND
Growth parameters at birth	ND	• Weight: 2.1 kg • Length: 37 cm • OFC: 35 cm	• Weight: 3.26 kg • Length: 41 cm • OFC: 39.5 cm	ND	• Weight: 2.6 kg • Length: 37 cm • OFC: 37 cm
Growth parameters at specified age	At age 4.75 yrs: • Weight: 8.82 kg • Length: 65 cm • OFC: 47.5 cm	At age 3.75 yrs: [7] • Weight: 6.5 kg • Length: 55 cm • OFC: 49 cm	See footnote 8.	ND	At age 9 yrs: • Weight: 4.7 kg • Length: 49 cm • OFC: 46.1 cm
Other		Intermittent exotropia	• Craniosynostosis • Renal calculi • Generalized joint hypermobility • Hip & knee flexion contractures		Renal calculi

ND = not documented; OFC = occipitofrontal head circumference
1. MacDonald et al [1989]
2. MacDonald et al [1989] (patient 2), Nikkel et al [2013]
3. Unpublished data are referenced describing a boy age 9 years with TD [Baker et al 1997]. No information regarding diagnostic features is reported, but the individual is reported to have been ventilated from birth, with severe developmental delay, hydrocephalus, hearing impairment, and acanthosis nigricans.
4. Nakai et al [2010]
5. Katsumata et al [1998], Kuno et al [2000]
6. Further deterioration by third decade of life and no longer able to use limbs or lift head
7. Growth parameter estimates based on growth charts
8. Slow linear growth, -6 to -6.5 SD below the mean on the achondroplasia growth charts; OFC at +1 SD in infancy and at -1.7 SD at age 8.7 years

Mosaicism. A female age 47 years who was mosaic for the common TD type 1-causing pathogenic variant p.Arg248Cys had asymmetric limb length, bilateral congenital hip dislocation, focal areas of bone bowing, an S-shaped humerus, extensive acanthosis nigricans, redundant skin folds along the length of the limbs, and flexion deformities of the knees and elbows [Hyland et al 2003]. She had delayed developmental milestones as a child. Academic achievements were below those of healthy sibs, but she is able to read and write and is employed as a factory worker. Her only pregnancy ended with the stillbirth at 30 weeks' gestation of a male with a short-limb skeletal dysplasia and pulmonary hypoplasia.

Takagi et al [2012] described an individual with somatic mosaicism for the p.Arg248Cys substitution in *FGFR3* (a pathogenic variant which typically results in TD type 1) who presented with features labeled as atypical achondroplasia.

Genotype-Phenotype Correlations

TD type 1. *FGFR3* pathogenic variants reported as causing the TD type 1 phenotype can be divided into three categories:

- **Missense variants** [Passos-Bueno et al 1999]. The two common variants p.Arg248Cys and p.Tyr373Cys probably account for 90% of TD type 1 [Xue et al 2014].
- **No-stop codon variants** represent fewer than 10% of TD type 1-causing variants (see Table 9).
- An **insertion variant** has been reported in one individual [Lindy et al 2016] (see Table 9).

TD type 2. A single *FGFR3* pathogenic variant (p.Lys650Glu) has been identified in all individuals with TD type 2 [Bellus et al 2000]. Other pathogenic variants at this position give rise to different phenotypes: p.Lys650Met has been identified in TD type 1, and p.Lys650Gln is seen in SADDAN (see Table 9).

Penetrance

The penetrance is 100%.

Nomenclature

Thanatophoric dysplasia was originally described as thanatophoric dwarfism, a term no longer in use. The descriptor "thanatophoric" is derived from the Greek for "death bearing," and refers to the very high incidence of perinatal death due to the multisystem complications of this condition. However, aggressive management has resulted in rare reports of long-term survivors, contradicting this initial description.

The lethal platyspondylic dysplasia (San Diego type) was previously considered a separate clinical entity, but is now recognized as the same condition as TD [Brodie et al 1999, Hall 2002].

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], TD type 1 is referred to as *FGFR3*-related thanatophoric dysplasia (type 1), and TD type 2 is referred to as *FGFR3*-related thanatophoric dysplasia (type 2); both are included in the *FGFR3* chondrodysplasias group.

Prevalence

The incidence of TD is reported to be 1:20,000 [Barbosa-Buck et al 2012] or higher (1:12,000 in Northern Ireland) in a population with optimized ascertainment [Donnelly et al 2010].

Genetically Related (Allelic) Disorders

FGFR3 pathogenic variants have been identified in several disorders with highly variable phenotypes (see Table 4a and Table 4b). Disorders included in Table 4a may have phenotypic features that overlap with thanatophoric dysplasia (TD) and should be considered in the differential diagnosis.

Table 4a. *FGFR3* Allelic Disorders to Consider in the Differential Diagnosis of Thanatophoric Dysplasia

Disorder	Comment	Distinguishing Clinical Features
Homozygous achondroplasia	• Typically lethal in perinatal period • Clinical presentation similar to TD, w/ short limbs & foramen magnum stenosis	• Family history of achondroplasia in both parents • These conditions can be impossible to distinguish on clinical & radiographic grounds.

Table 4a. continued from previous page.

Disorder	Comment	Distinguishing Clinical Features
SADDAN (*s*evere *a*chondroplasia w/ *d*evelopmental *d*elay & *a*canthosis *n*igricans) (OMIM 616482)	• Rare disorder characterized by extremely short stature, severe tibial bowing, seizures, foramen magnum stenosis, hydrocephalus, structural brain malformations, developmental delay, & acanthosis nigricans • Caused by *FGFR3* pathogenic variant p.Lys650Met [1]	• Tibial bowing • Clavicular bowing • Unlike TD, persons w/SADDAN dysplasia often survive beyond infancy w/o ventilatory support. However, respiratory support or ventilation may be required in neonatal period & neonatal death is reported.

1. Bellus et al [1999], Tavormina et al [1999]

Table 4b. *FGFR3* Allelic Disorders Not in the Differential Diagnosis of Thanatophoric Dysplasia

Disorder	Associated *FGFR3* Pathogenic Variant(s)
Achondroplasia	p.Gly380Arg & p.Gly375Cys (identified in nearly 100% of persons w/achondroplasia) [1]
Hypochondroplasia	~80% of persons w/hypochondroplasia have an identified *FGFR3* pathogenic variant.
Crouzon syndrome w/acanthosis nigricans [2]	p.Ala391Glu
Familial acanthosis nigricans	p.Lys650Thr was identified in several affected family members w/AD acanthosis nigricans & short stature.
Muenke syndrome [2]	p.Pro250Arg [3]
Lacrimoauriculodentodigital (LADD) syndrome (OMIM 149730) (aka Levy Hollister syndrome)	p.Asp513Asn reported in 1 family [4]
Camptodactyly, tall stature, & hearing loss syndrome (OMIM 610474)	p.Arg621His [5]

AD = autosomal dominant

1. Camera et al [2001] reported an individual with the common TD type 1-causing variant p.Arg248Cys and a clinical phenotype of achondroplasia. Although mosaicism remains a possible explanation for the mild phenotype, no mosaicism was identified in either buccal mucosal cells or blood.

2. See *FGFR* Craniosynostosis Syndromes Overview.

3. Passos-Bueno et al [1999], McIntosh et al [2000]

4. Rohmann et al [2006]

5. A dominant-negative mechanism is suspected to cause decreased *FGFR3* function in this condition [Toydemir et al 2006].

Differential Diagnosis

Table 5. Other Genes of Interest in the Differential Diagnosis of Thanatophoric Dysplasia

Gene(s)	Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/TD	Distinguishing from TD
CFAP410 *CEP120* *DYNC2H1* *DYNC2I1* *DYNC2I2* *DYNC2LI1* *IFT52* *IFT80* *IFT81* *IFT122* *IFT140* *IFT172* *KIAA0586* *KIAA0753* *NEK1* *TRAF3IP1* *TCTEX1D2* *TTC21B* *WDR19* *WDR35*	Skeletal ciliopathies: incl perinatal lethal short-rib polydactyly syndromes & Jeune asphyxiating thoracic dystrophy (See OMIM PS208500.)	AR Digenic [1]	• May be lethal in perinatal period or infancy • Narrow thorax & short ribs; short stature & short limbs noted in infancy (But survivors may manifest only mild-to-moderate short stature.)	• Polydactyly & wide variety of multisystem features common; may involve cardiac, renal, liver, pancreatic, intestinal, genital, retinal, & ectodermal tissues [2] • Improvement in respiratory status occurs in some survivors w/skeletal ciliopathies, & persons may manifest only mild-to-moderate short stature.
COL1A1 *COL1A2*	Perinatally lethal osteogenesis imperfecta [3] (previously OI type II) (See *COL1A1/2*-OI.)	AD	• Typically lethal in perinatal period • Markedly shortened & bowed long bones; severe short stature	• Absence of severe micromelia; craniosynostosis; small iliac bones, narrow sacroiliac notch, & platyspondyly; bowing more significant than in TD • Note: TD is not assoc w/ undermineralization, fractures, wormian bones, dentinogenesis imperfecta, or dark blue sclera.
COL2A1 *SLC26A2* *TRIP11*	Achondrogenesis (ACG) type IA, type IB, & type II (OMIM PS200600)	AR AD	• Typically lethal in perinatal period • Short stature w/ micromelia, relative macrocephaly, short ribs, & brachydactyly	• Minimal or absent ossification of vertebral bodies, iliac, & ischial bones in ACG • Rib fractures in type II ACG • Distinctive facial features, short neck w/excess soft tissue
COL2A1	Platyspondylic lethal skeletal dysplasia, Torrance type (PLSD-T) [4] (OMIM 151210)	AD	• Typically lethal in perinatal period • Short long bones w/ragged metaphyses, platyspondyly, & short ribs	• Bowed radius/tibia may be present. • PLSD-T can be differentiated histologically by presence of dilated loops of endoplasmic reticulum in chondrocytes.
FGFR3	Homozygous achondroplasia	Codominant	See Allelic Disorders.	See Allelic Disorders.
	SADDAN	AD		

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/TD	Distinguishing from TD
GPX4	Spondylometaphyseal dysplasia, Sedaghatian type (OMIM 250220)	AR	• Typically lethal in perinatal period • Short long bones, metaphyseal abnormalities, cupped ribs, platyspondyly, brachydactyly • Cerebral ventriculomegaly, other CNS abnormalities	• Irregular ("lacy") ossifications in iliac wings & calcaneus • Disproportionately long fibulae • Cardiac anomalies incl structural congenital heart disease
HSPG2	Dyssegmental dysplasia, Silverman-Handmaker type (OMIM 224410)	AR	• Typically lethal in perinatal period • Narrow thorax, short stature, bowed limbs	• Spine anisospondyly is present. • Cleft palate & encephalocele may be present.
INPPL1	Opsismodysplasia (OMIM 258480)	AR	• May be lethal in perinatal period • Short long bones, platyspondyly, relative macrocephaly, small chest	Delayed bone maturation & poor bone quality
PAM16	Spondylometaphyseal dysplasia, Megarbane-Dagher-Melike type (OMIM 613320)	AR	• May be lethal in perinatal period • Short limbed short stature, narrow chest w/short ribs, narrowed cervical canal, platyspondyly • Frontal bossing, depressed nasal bridge • Developmental delay • Hearing impairment	• Absence of epiphyseal ossification of the knees • Square iliac bones • Horizontal acetabulae w/medial & lateral spurs • Hypoplastic ischia
PEX7	Classic rhizomelic chondrodysplasia punctata type 1 (RCDP1)	AR	• Most affected children do not survive 1st decade of life; a proportion die in the neonatal period. • Rhizomelia, punctate calcifications in cartilage w/epiphyseal & metaphyseal abnormalities, coronal cleft or notch of vertebral bodies • Brain malformations	• Punctate epiphyseal dysplasia evident as stippled epiphyses on radiography; coronal vertebral clefts may be present. • Rhizomelia prominent (compared to micromelia in TD) • Birth weight, length, & head circumference often at lower range of normal • Cataracts usually present at birth or in 1st few mos of life
SLC35D1	Schneckenbecken dysplasia (OMIM 269250)	AR	• Typically lethal in perinatal period • Short-limbed short stature • Platyspondyly	• Hypoplastic iliac bones w/ characteristic appearance resembling a snail • Broad long bones • Precocious ossification of the tarsus • Hydrops

Table 5. continued from previous page.

Gene(s)	Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/TD	Distinguishing from TD
SOX9	Campomelic dysplasia (CD)	AD	• Typically lethal in perinatal period • Variable stature (short to normal), w/short limbs & narrow thorax	• Profound hypoplasia of the body of the scapulae (compared to globally small scapulae in TD) • Tibial & femoral bowing (w/ longer femurs compared to TD) • Tubular bones are poorly developed & show immature ossification, w/nonossification of thoracic pedicles. • Many have 11 pairs of ribs. • Skin dimples are often present. • ≤75% of persons w/CD w/a 46,XY karyotype have either female external genitalia or ambiguous genitalia.

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; TD = thanatophoric dysplasia

1. Biallelic inheritance of pathogenic variants in *DYNC2H1* and *NEK1* has been reported (see OMIM 613091).

2. Huber & Cormier-Daire [2012]

3. Clinically, osteogenesis imperfecta (OI) was classified into four types; the type most reminiscent of TD is OI type II (perinatally lethal OI).

4. The Luton type is considered to be a mild form of the Torrance type [Nishimura et al 2004].

Management

Evaluations Following Initial Diagnosis

Diagnosis of thanatophoric dysplasia (TD) most often occurs prenatally. When TD has been diagnosed prenatally, referral should be made to a maternal-fetal medicine specialist for assessment and management advice (see Pregnancy Management).

Long-term survivors are rare and require aggressive intervention for complications of the condition. The family should be informed of prognosis on the basis of the reports of complications in long-term survivors.

Table 6, Table 7, and Table 8 are only relevant to the small number of long-term survivors. To establish the extent of disease and needs in a newborn diagnosed with thanatophoric dysplasia (TD), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Thanatophoric Dysplasia

System/Concern	Evaluation	Comment
Respiratory	• Assessment of respiratory rate, skin color, & oxygen saturations • Arterial blood gases may be helpful in infants who survive immediate postnatal period. • Polysomnography • Assessment for foramen magnum stenosis	If tracheostomy & long-term ventilatory support is considered, consult w/respiratory physician & multidisciplinary team w/ expertise in tracheostomy care.

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Foramen magnum narrowing, hydrocephalus, &/or other CNS abnormalities	Head & spine CT or MRI	• Brain stem compression may contribute to respiratory insufficiency. • Cervical myelopathy may → quadriplegia.
Craniosynostosis	Head CT in persons w/clinical evidence of craniosynostosis	
Seizures	Consider assessment w/neurologist &/or EEG if episodes suspicious for seizures.	
Audiology	Audiologic assessment	
Ophthalmology	Ophthalmology eval for exotropia	
Developmental delay	Developmental assessment	
Genetic counseling	By genetics professional [1]	To inform affected persons & families re nature, MOI, & implications of TD to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

CNS = central nervous system; MOI = mode of inheritance; TD = thanatophoric dysplasia
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse.

Treatment of Manifestations

Decisions about management should be made following consultation with parents and a discussion of the complications, clinical course, and prognosis of the condition. Considerations may include the parents' desire for extreme life-support measures or provision of comfort care for the newborn.

Table 7. Treatment of Manifestations in Individuals with Thanatophoric Dysplasia

Manifestation/Concern	Treatment	Considerations/Other
Respiratory insufficiency	Neonates typically require aggressive respiratory support (e.g., ventilation, tracheostomy) to survive.	1 long-term survivor required supplemental oxygen in neonatal period & ventilatory support from age 2 mos. [1]
Perioperative management [2]	• Assessment of pulmonary function • Assessment of previous spine imaging for "spine at risk" findings • Availability of ICU care • Availability of anesthesia staff w/experience in mgmt of skeletal dysplasias • Maintenance of cervical spine in a neutral position (may require intubation using specialized intubation equipment) • Consideration of spinal monitoring during the procedure to evaluate safety during intraoperative manipulations	Use of evoked potential monitoring requires avoidance of volatile anesthetic agents & muscle relaxants, which could affect evoked potential recordings.
Hydrocephalus	Eval by neurosurgeon for shunt placement	

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Craniocervical junction constriction	• Eval by neurosurgeon for suboccipital decompression • Standard mgmt of complications of spinal cord compression such as spasticity	Surgical decompression may only provide temporary benefit, w/return of respiratory insufficiency & neurologic compromise. [1, 3]
Seizures	Standard anti-seizure treatment	
Hearing impairment	Hearing aids per audiologist &/or otolaryngologist	
Vision	Mgmt of exotropia by ophthalmologist	
Development	Individualized developmental support by allied health clinicians	

1. Nikkel et al [2013]
2. Consensus perioperative management guidelines for individuals with skeletal dysplasia have been published [White et al 2017].
3. MacDonald et al [1989]

Surveillance

Table 8. Recommended Surveillance for Individuals with Thanatophoric Dysplasia

System/Concern	Evaluation	Frequency
Respiratory insufficiency	• Assessment of respiratory status • Neuroimaging in event of respiratory deterioration to evaluate for compression of brain stem at craniocervical junction	Annual clinical eval in long-term survivors
Neurologic complications	• Assessment of neurologic status • EEG in event of seizure activity • Neuroimaging if signs/symptoms of spinal cord compression	Annual clinical eval for signs & symptoms in long-term survivors
Joint contracture or joint hypermobility	Orthopedics eval	Annual clinical eval in long-term survivors
Hearing impairment	Audiology assessment	
Vision	Ophthalmology eval	
Development	Developmental assessment	

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

When TD has been diagnosed prenatally, referral should be made to a maternal-fetal medicine specialist for assessment and management advice. Potential pregnancy complications include prematurity, polyhydramnios, malpresentation, and cephalopelvic disproportion caused by macrocephaly from hydrocephalus or a flexed and rigid neck. Cephalocentesis and cesarean section may be considered to avoid maternal complications.

Management of an affected pregnancy is determined following discussion between the medical team and family regarding prognosis and the need for aggressive life-saving measures in survivors. This is often center-specific. Indicators of lethality on ultrasound can provide additional information.

Consensus guidelines on perinatal management of skeletal dysplasias have been published [Savarirayan et al 2018]. Management considerations can be addressed on three levels:

- **Maternal.** Surveillance for cephalopelvic disproportion, polyhydramnios, and/or preterm labor; avoidance of emergency C-section for fetal distress
- **Fetal.** Surveillance for malpresentation, periodic prenatal ultrasound monitoring of head circumference, MRI for fetal lung volume, and/or fetal stress testing
- **Perinatal.** Establishment of a plan for assessment, care, and/or withdrawal of care after delivery. Postnatal clinical and radiographic assessment should occur. In terminated pregnancies, postmortem evaluation including radiography and storage of DNA in case of diagnostic uncertainty should be discussed.

Therapies Under Investigation

Over the past five years several new precision therapies have begun to emerge for achondroplasia (an allelic *FGFR3* skeletal dysplasia) that are now in Phase II and Phase III human clinical trials. These new therapeutic approaches include: use of C-type natriuretic peptides (CNP) to modulate downstream *FGFR3* signaling [Savarirayan et al 2019a, Breinholt et al 2019], blocking of *FGFR3* using selective tyrosine kinase inhibitors [Komla-Ebri et al 2016], and ligand traps to decrease the quantity of growth factors able to bind to mutated FGFR3 receptors [Garcia et al 2013]. These treatments could also be effective for TD, given a similar underlying molecular mechanism [Savarirayan et al 2019b], but how this very severe phenotype would be modified is currently unknown.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Thanatophoric dysplasia (TD) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Almost all probands reported to date with TD represent simplex cases (i.e., the only affected family member) and have the disorder as a result of a *de novo FGFR3* pathogenic variant. The parents of a proband with a *de novo FGFR3* pathogenic variant are not affected.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant to confirm the genetic status of the parents and to facilitate reliable recurrence risk assessment.
- If the *FGFR3* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with somatic and/or germline mosaicism. (Note: Parental somatic mosaicism is difficult to detect in leukocyte DNA using standard molecular genetic techniques.)

- Somatic and germline mosaicism for the p.Arg248Cys *FGFR3* pathogenic variant was reported in a parent with a skeletal dysplasia; this individual's only offspring had a lethal skeletal dysplasia with findings consistent with TD [Hyland et al 2003].
- Although no instances of mosaicism in an individual without signs of a skeletal dysplasia have been reported in the literature, it remains a theoretic possibility.

- An advanced paternal age effect has been reported [Donnelly et al 2010].

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *FGFR3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent and neither parent has signs of a skeletal dysplasia, the recurrence risk to sibs is presumed to be low but slightly greater than that of the general population because of the possibility of parental mosaicism [Hyland et al 2003].

Offspring of a proband. Individuals with TD do not reproduce.

Other family members. Extended family members of the proband are not at increased risk.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies. Once the *FGFR3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for TD are possible.

Low-risk pregnancies. Routine prenatal ultrasound examination may identify skeletal findings (e.g., cloverleaf skull, very short extremities, small thorax) that raise the possible diagnosis of TD in a fetus not known to be at risk. Once a lethal skeletal dysplasia is identified prenatally, it is often difficult to pinpoint a specific diagnosis. Consideration of molecular genetic testing for *FGFR3* pathogenic variants in these situations is appropriate.

Cell-free DNA testing techniques have been reported for noninvasive prenatal diagnosis of TD [Chitty et al 2015, Zhang et al 2019].

Note: When TD has been diagnosed prenatally, referral should be made to a maternal-fetal medicine specialist for assessment and management advice (see Pregnancy Management).

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Born a Hero**
  www.bornahero.org
- **MedlinePlus**
  Thanatophoric dysplasia

- **Compassionate Friends**
  Supporting Family After a Child Dies
  Phone: 877-969-0010
  compassionatefriends.org
- **Helping After Neonatal Death (HAND)**
  PO Box 341
  Los Gatos CA 95031
  Phone: 888-908-HAND (4263)
  www.handonline.org
- **Medline Plus**
  Dwarfism
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Thanatophoric Dysplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR3	4p16.3	Fibroblast growth factor receptor 3	FGFR3 @ LOVD	FGFR3	FGFR3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Thanatophoric Dysplasia (View All in OMIM)

134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3
187600	THANATOPHORIC DYSPLASIA, TYPE I; TD1
187601	THANATOPHORIC DYSPLASIA, TYPE II; TD2

Molecular Pathogenesis

FGFR3 encodes fibroblast growth factor receptor 3 (FGFR3), a negative regulator of bone growth during ossification [Cohen 2002]. Mice with knockout variants of *Fgfr3* have expanded growth plates and are overgrown, with elongated vertebrae, femurs, and tails.

Pathogenic variants in *FGFR3* are gain-of-function variants that facilitate dimerization and activation of FGFR3 in the absence of ligand binding [Baitner et al 2000, Cohen 2002]. This constitutional activation leads to premature differentiation of proliferative chondrocytes into prehypertrophic chondrocytes, and ultimately to premature maturation of the bone [Cohen 2002, Legeai-Mallet et al 2004].

FGFR3-related skeletal dysplasias display a spectrum of phenotypic severity. The level of increased tyrosine kinase activity conferred by different *FGFR3* pathogenic variants correlates with the severity of disorganization of endochondral ossification and, therefore, with the skeletal phenotype [Bellus et al 1999, Bellus et al 2000, Foldynova-Trantirkova et al 2012].

Mechanism of disease causation. Gain of function.

- Of note, no-stop variants resulting in protein extension are associated with thanatophoric dysplasia (TD).
- Missense variants causing TD type 1 introduce a cysteine (Tyr373Cys, Arg428Cys) resulting in dimerization by covalent bonding (see Genotype-Phenotype Correlations).
- Missense variants involving residue 650 (e.g., Lys650Met [TD type 1] or Lys650Glu [TD type 2]) mimic conformational changes in the tyrosine kinase domain, which mimic the conformational changes that occur with ligand binding.
- The p.Lys650Glu pathogenic variant causing TD type 2 has been shown to cause accumulation of intermediate, activated forms of FGFR3 in the endoplasmic reticulum [Lievens & Liboi 2003]. It is unclear how this may contribute to the more severe phenotype in TD type 2.

Table 9. Notable *FGFR3* Pathogenic Variants

Reference Sequences	Phenotype	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000142.3 NP_000133.1	TD type 1	c.742C>T	p.Arg248Cys	One of the most common pathogenic variants [Xue et al 2014] [1]
		c.742_743insTGT	p.Arg248delinsLeuCys	Insertion variant [Lindy et al 2016] [1]
		c.1108G>T	p.Gly370Cys	See Table 3.
		c.1118A>G	p.Tyr373Cys	One of the most common pathogenic variants [Xue et al 2014] [1]
		c.1949A>T	p.Lys650Met	
		c.2420G>T	p.Ter807LeuextTer101	No-stop variants → protein extension [1, 2]
		c.2419T>G	p.Ter807GlyextTer101	
		c.2419T>C	p.Ter807ArgextTer101	
		c.2419T>A	p.Ter807ArgextTer101	
		c.2421A>T	p.Ter807CysextTer101	
		c.2421A>C	p.Ter807CysextTer101	
		c.2421A>G	p.Ter807TrpextTer101	
	TD type 2	c.1948A>G	p.Lys650Glu	In all persons w/TD type 2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. Also known as non-stop variants.

Chapter Notes

Author History

Garry R Cutting, MD; Johns Hopkins University (2004–2020)
Tegan French, BMBS (2020–present)
Barbara Karczeski, MS, MA; Johns Hopkins University (2004–2020)
Ravi Savarirayan, MBBS, MD, FRACP, ARCPA (Hon) (2020–present)

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